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PRIOR ART. That discussion includes in particular references to the work of Dr. Kwok-Hung Sit, one of the inventor Applicants of this invention.

Additionally, as noted above, the method of this invention provides the place for a variable, generic sequence, and teaches how these other therapeutic agents may be incorporated in place of the generic sequence to customize the therapeutic applications.

The importance of flanking sequences around CpG is very crucial and results in a specific biological activity, Krieg, A.M. et al., Nature, 374, 546, -549, 1995; Yamamoto, S. et al., Curr. Top. Microbial. Immunol. 247, 23-39, 2000. Bauer, S. et al., Proc. Natl. Acad. Sci., USA, 98, 9237-9242, 2001.

Therefore, in sum, the Applicants submit that the amended claims 21-22 and 36-37 address the above concerns expressed in the Office Action as to the second grounds of rejection under U.S.C. Section 112, First Paragraph.

**Further Discussion of the Prior Art
and**

Detailed experimental results by Applicants for colon cancer

The discussion below pertains to the prior art relied on in the Office Action.

Detailed experimentation was carried out by Applicants for colon cancer as disclosed in the specification as filed and summarized in the next three paragraphs.

One of the inventors, Dr. Sit, L. Qi and K.H. Sit, Molecular Cell Biology Research Comm., 23, 319-327, 2000, showed that a number of house keeping genes have canonical CpG islands at 5'- promoter region, which are critical in regulation of vital intermediary metabolism and cell structure, whose loss or alteration is central to cell death. House keeping genes such as the gene controlling energy production in glycolysis, tricarboxylic acid cycle (TCA cycle; essential in ATP production), respiratory

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electron transport chain. Gene for pyruvate dehydrogenase , whose down regulation causes cell acidification . Basal histone genes, H2A.X , which regulates nucleosome assembly. In this publication it was shown that critical differential gene activity is caused by CpG specific modulation. Such CpG specific modulation was also shown earlier to regulate gene function without changing the informational contents of the genetic code, Razin , A., and Riggs, A.D., Science, 210,604-610, 1980; Falls, J.G., Pulford, D.F., Wylie, A.A., Jirtle, R, Am. J. Patho., 154, 635-647,1999; Jones, P.A., Trends in Genetic, 15, 4310-435, 1999.

It was shown by several authors, that unmethylated CpG islands in the 5'-promoter and intronic sites of transcriptionally active genes are concentrated in the euchromatin domain , which are also susceptible to nucleases , Feil, R. and Khosla, S. Trends Genet., 15, 34-37, 1999; Ng, H.H. and Bird, A., Curr. Opin. Genet. Dev., 9, 158-153, 1999, Bird, A., Trend Genet., 11, 94-100, 1995. It was also shown that CpG methylation confers nuclease resistance to such genes.

Another publication by Dr. Sit, L. Qi and K.H. Sit, Molecular Cell Biology Research Comm., 23, 319-327, 2000, where detailed analysis of a number of the house keeping genes was carried out. The genetic regulation of glycolysis, the tricarboxylic acid cycle (TCA, citric acid or Krebs cycle) and respiratory electron transport chain involving glucose catabolism and energy requirement of cell. Puruvate dehydrogenase gene regulation was shown to have essential role in this path. And loss of such regulation leads to mitochondrial disfunction.

CpG oligonucleotides selected from such House keeping gene pool which have CpG islands in the promoter region were selected in our earlier studies; L. Qi and K.H. Sit, Molecular Cell Biology Research Comm., 3, 319-327, 2000, and L. Qi and K.H. Sit, Molecular Cell Biology Research Comm., 3, 33-41, 2000. It has been shown in the cited

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publications that in mammals caspase dependent and independent pathways are responsible for cell death or apoptosis. In our studies cited in publications cited above, it was shown that CpG ODN block apoptosis. It was further demonstrated that by reversing the CpG motif, viz., GpC or methylation of cytidine, i.e., 5-methylCpG motifs are ineffective in preventing such apoptosis.

CONCLUSION

Applicants believe that by amending the majority of the claims to method claims and amending the product into narrow claims resulting strictly from the application of the disclosed novel method, they have addressed the concerns expressed in the Office Action of 2/26/08.

A Notice of Allowance is respectfully requested. The Examiner is requested to kindly contact the undersigned representative if this communication does not place the case in condition for allowance.

Respectfully submitted,
Suresh C. Srivastava
Satya P. Bajpai
Kanchi Lingam, Applicants

By: 

Indu M. Anand
Registration Number: 52,557
15 Green Way
Chelmsford, MA 01824
(978) 250-9003/ (617) 930-5000